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METHODOLOGY FOR THE USE OF PRIMATES IN THE EXPLORATION OF HAZARDOUS ENVIRONMENTS

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Methodology used in nonhuman primate research varies considerably because of the wide variety of questions to be resolved with use of these subjects. Hazardous environments that have a high probability of being lethal are explored, using techniques similar to the classical pharmacologic screening studies employed to determine the amount of a compound that is a lethal dose for 50% of the subject population (LD_{50}). The analyses of these environments rarely require sophisticated methodology. The physical characteristics of the hazards can be specified, model environments constructed, and lethality assessed, following a routine exposure using nominally healthy (research grade) nonhuman primates. Commonly used experimental designs for these exploratory research projects involve control and experimental groups in a pre- versus post-exposure survival testing.

Less hazardous environments with lower probabilities of lethality pose special problems of assessment because the results of the exposures are less likely to produce such grossly observable changes. Environments, however, need not be lethal to be of vital concern. Lethality represents one end of a continuum of behavior to be measured that extends to 1) serious nonlethal environments involving irreversible incapacitation; 2) less serious temporary, but total, incapacitation; 3) performance decrements; and, 4) finally, at the other end of this continuum, the sensory detection of an unusual environment.

The exploration of these hazardous environments requires research with nonhuman primates in a variety of situations. The investment of resources also varies considerably in the determination of the degree of precision required. Prior to the discussion of the more sophisticated behavioral assessment, let us examine the simple screening methods.

Preliminary Simple Screening Experiments

The behavioral hazard of an environment cannot be assessed until some parameters are known: First, and usually easiest, determination of the lethal dose (LD_{50}) should be calculated, and second, this measurement should be followed with a determination of the variability of that mean value. The standard deviation (sigma) is a valuable statistical tool to use as a supplement to the information obtained with the LD_{50}. Third, given the mean (LD_{50}) and sigma, the fiducial limits can be calculated for any probability limit.

All these screening experiments, obviously, can be conducted on untrained animals of research quality at minimal cost. Results of these screening experiments provide valuable data that allow the approximation of exposure levels calculated to produce sublethal behavioral perturbations. Because the research costs increase rapidly with attempts to identify precisely the magnitude and duration of the effects of a hazardous environment, it is important to make every effort to extract a maximum amount of information from the screening experiment. Hence, there is value in gross observations of the behavior of the subjects during the LD_{50} determinations. These observations may lead to working hy-

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potheses about the nature of the incapacitation, including sense modalities and behaviors likely to be influenced by the insult.

As a final point on the preliminary screening experiments, both Hofer and Kratochvil have commented in this monograph on the dangers of extrapolation between species.

One assumes a greater risk with the more expensive behavior decrement subhuman primate experiments, unless the LD_{50} has been carefully calculated on the same species.

*Behavior Decrement Determinations**

The more complex methodolgy required to assess performance decrements requires a significant increase in time and effort. While the screening experiments require only research grade, acclimated primates, the background training time required to obtain asymptotic performance often consumes several months following the assignment of research-grade primates to the project. The preexperiment training time is dependent largely upon the degree of complexity of the primate behavior that is required to answer the questions about the environment.

The experiments on rapid decompression of Koestler (1965, 1967) are examples of this kind of research. Briefly, the problem posed to these investigators concerned the behavioral response to a near vacuum. The goal of this assessment was to determine the following: 1) time of useful consciousness following the onset of the decompression; 2) time of total behavioral incapacitation; 3) time of performance decrement following the recovery from total incapacitation; and 4) time to return to baseline levels of performance efficiency. To answer these questions, a group of chimpanzees was taught to perform several tasks. The performance panel is shown in FIGURE 1.

The tasks are as follows: 1) auditory cue reaction time; 2) visual cue reaction time, pushbutton response; 3) visual cue reaction time, lever response; 4) concept of odd task; and 5) continuous avoidance task. With these quantifiable behavioral measurements, precise answers to questions concerning the effects of rapid decompression can be provided.

FIGURE 2 shows a diagram of the environment to be evaluated. It should be noted that the experiment starts as the altitude chamber door is sealed. Two pre-exposure behavioral tests were conducted in the ambient pressure and approximately 100% oxygen environment, and one behavioral test at 179 mm Hg and approximately 100% oxygen. These baseline tests were followed by the rapid decompression and recompression exposure, which happened during the fourth behavioral test. Behavioral testing continued with appropriate rest periods until preexposure baseline criteria were reachieved, or 24 hours postexposure, at which time the test was discontinued.

An example of the performance of the continuous-avoidance task during a rapid-decompression experiment is shown in FIGURE 3. Preexposure responses were recorded as upward excursions of the pen on this record, and the horizontal excursions indicate no response during that time period. Note the stable preexposure performance, the brief period of useful consciousness, the time of total incapacitation, time of performance decrement, and, finally, recovery to baseline levels of performance.

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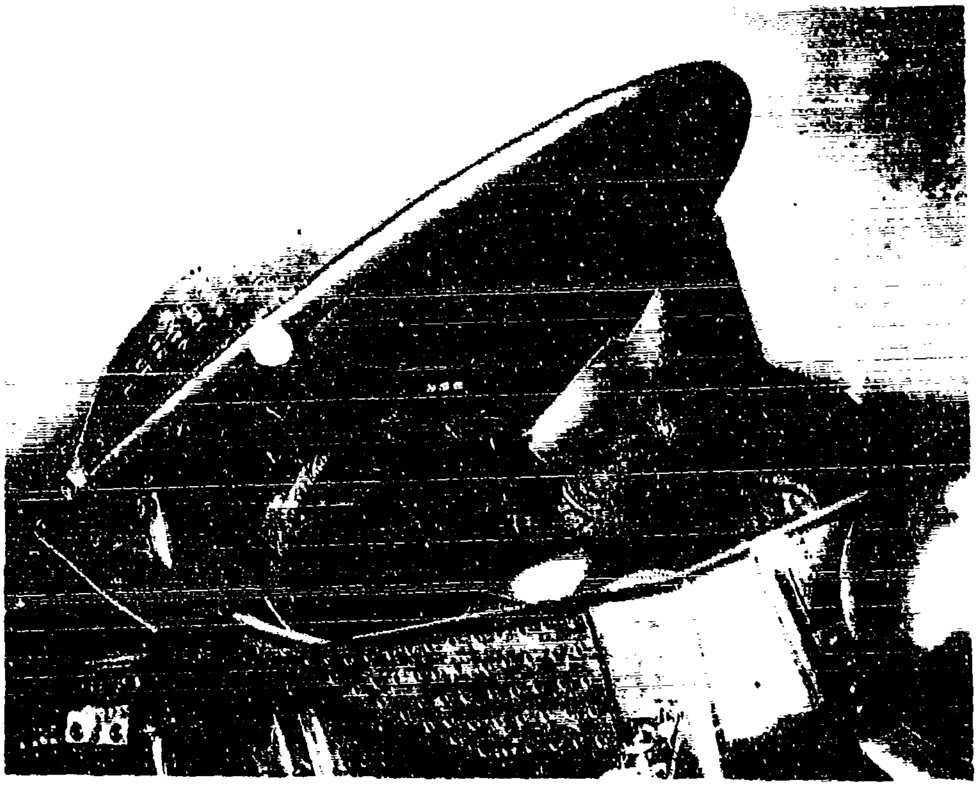

FIGURE 1. The restrained chimpanzee for rapid decompression tests.

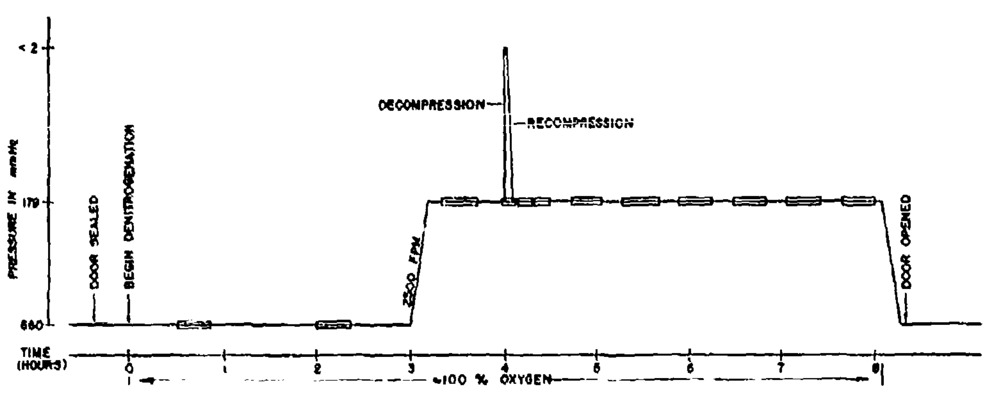

FIGURE 2. The environmental pressure profile for the rapid decompression test.

The second experiment that I would like to discuss concerns the methodology required to assess another nonlethal, but hazardous, environment. Sufficiently high-intensity light flashes produce burns on the retina of primates, and large lesions are easily detected with the ophthalmoscope. Determinations of total blindness or total loss of foveal vision can be made using the naive research-grade primate in the screening type experiment. And, indeed, many experiments have been accomplished with use of this method. The results show the amount of

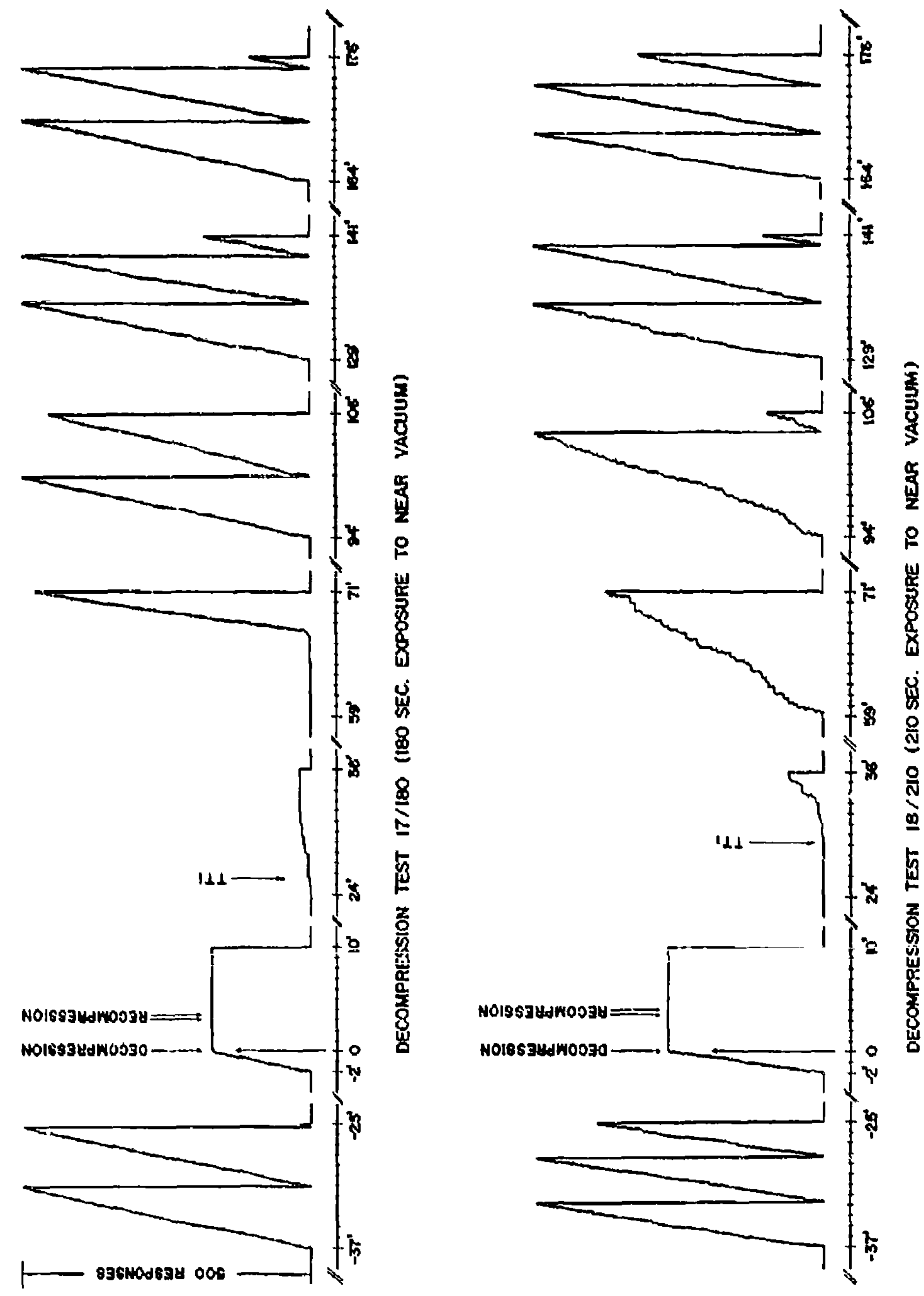

FIGURE 3. Two examples of lever-pressing behavior during rapid decompression tests.

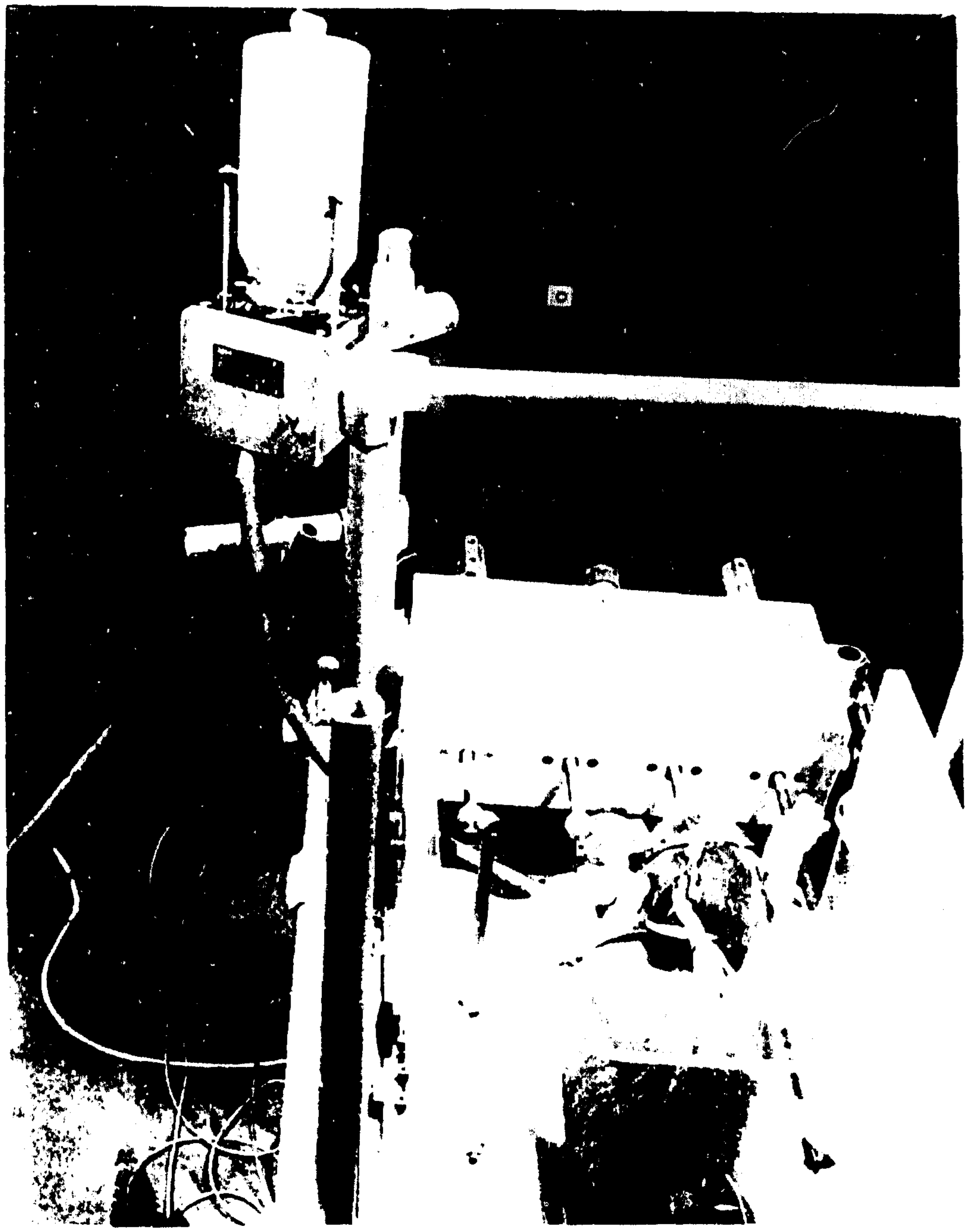

FIGURE 4. The subjective visual-acuity test environment.

energy that must be delivered in order to produce a lesion on the retina of a rhesus monkey. However, this ophthalmoscopic method will not allow an assessment of a decrement in subjective visual acuity.

Thus, a more complex behavioral method had to be applied in order to determine the changes in visual acuity that accompany retinal lesions.

Farrer and Graham (1967) developed a monocular and binocular technique for determining subjective visual acuity in the rhesus monkey. Basically, the monkeys were taught to discriminate between a series of Landolt rings. FIGURE 4

shows a picture of this research situation. The animals were shown a Landolt ring and given an opportunity to press one of four levers.

If the animal could see the position of the break in the ring and press the lever associated with that position, a food reward was delivered. By making the ring smaller and smaller, a threshold for visual acuity was obtained. By covering one eye, monocular visual acuity was obtained, an example of which is shown in

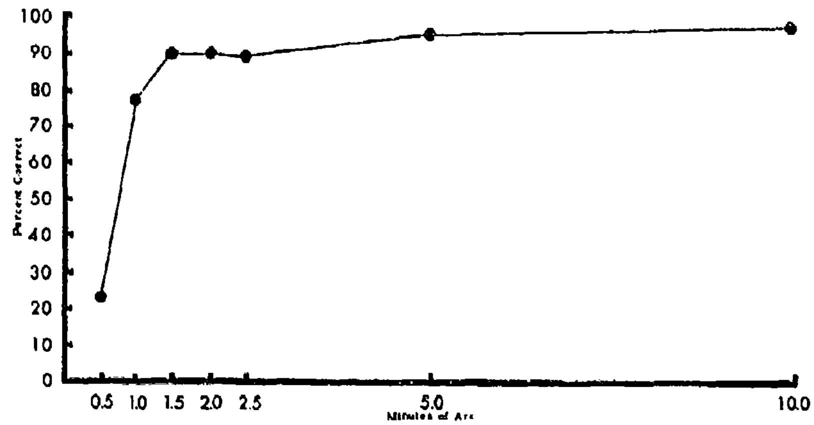

FIGURE 5. Performance accuracy (percent correct) at each viewing angle of the subjective visual-acuity test.

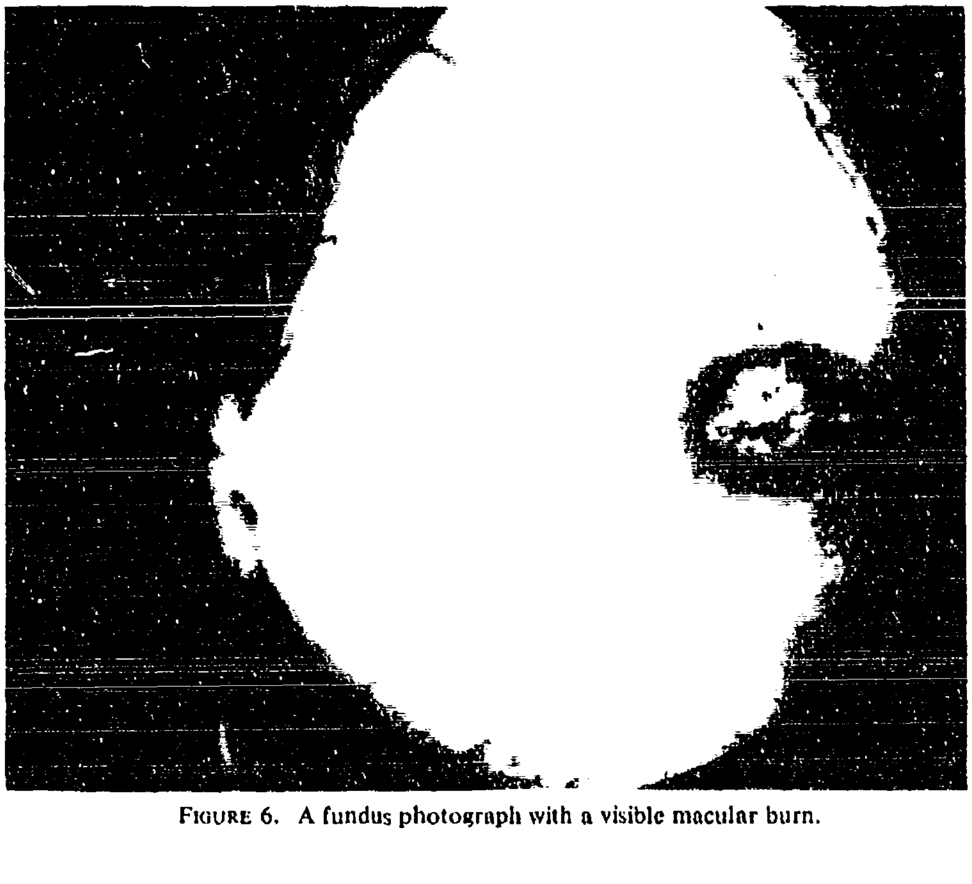

FIGURE 6. A fundus photograph with a visible macular burn.

FIGURE 7. A fundus photograph of a rhesus monkey retina exposed to 80% of the energy required to produce a lesion.

FIGURE 5. As this figure shows, a performance is quite good as long as the stimuli are above 20/20 (1 minute of arc) for this emmetropic monkey. Following the production of a lesion† shown in FIGURE 6, visual acuity changed to approximately 20/50. How much vision remains with a partially intact macula cannot be determined without the subjective acuity testing.

The fundus shown in FIGURE 7 was exposed to 80% of the energy required to produce an ophthalmoscopically observable lesion, and this subject demonstrated no loss of acuity as a result of that exposure. The fundus shown in FIGURE 8 was exposed to 50% of the energy required to produce an observable lesion, and, again, no visual acuity decrement was observed.

The third and last example of behavioral methodology concerns the detection of auditory stimuli. The assessment of acoustically traumatic environments can be accomplished by routine otological examination and necropsy following an exposure to this potentially hazardous environment, if the interest is confined to anatomical changes. However, if the research objectives include an attempt to answer questions about the effects of hazardous environments on sensory perception or capacity to work following a dangerous exposure, it becomes necessary

† Dr. Walter J. Geeraets of the Medical College of Virginia made the experimental lesions in all the subjects, using special equipment designed and constructed by Dr. W. T. Ham and Mr. Ray Williams. The subjective visual acuity determinations were made by Dr. Ernest S. Graham of Washington State University, Pullman, Wash., under Air Force contract no. F29600-67-C-0024.

to develop techniques in addition to standard anatomical inspection. Auditory sensitivity of rhesus monkeys to pure-tone stimuli has been evaluated by the use of summed evoked cortical responses as well as operant behavioral techniques providing audiograms (before and after exposures) for these primates.

FIGURE 9 is a picture of the rhesus monkey in the experimental situation ready for audiogram testing, which was accomplished by Dalton (1967). The lever pressing behavior shown in FIGURE 10 was rewarded with a food pellet (delivered at variable intervals), but at random times during this lever-pressing sequence a tone was presented to the subject through the speaker in the headset. This tone signified the impending unavoidable shock delivered 20 seconds following the onset of the tone. Normally, the animal stops pressing the lever as soon as he hears the tone and remains still until the shock is delivered, at which time he resumes lever-pressing behavior.

This record shows the stable and consistent lever-pressing behavior of this subject, except during those presentations of the tones that are above threshold. Thus, with this method, audiograms can be obtained by successive presentations of various pure tones at several intensity levels. The last figure shows audiograms from two rhesus monkeys. These audiograms show atypically high thresholds at 2,000 cycles per second. Further examination revealed that one subject had a conductive hearing loss, and the other was tested in a free field with a standing wave which produced the perturbation.

In summary, three behavioral methods for the exploratory investigation of

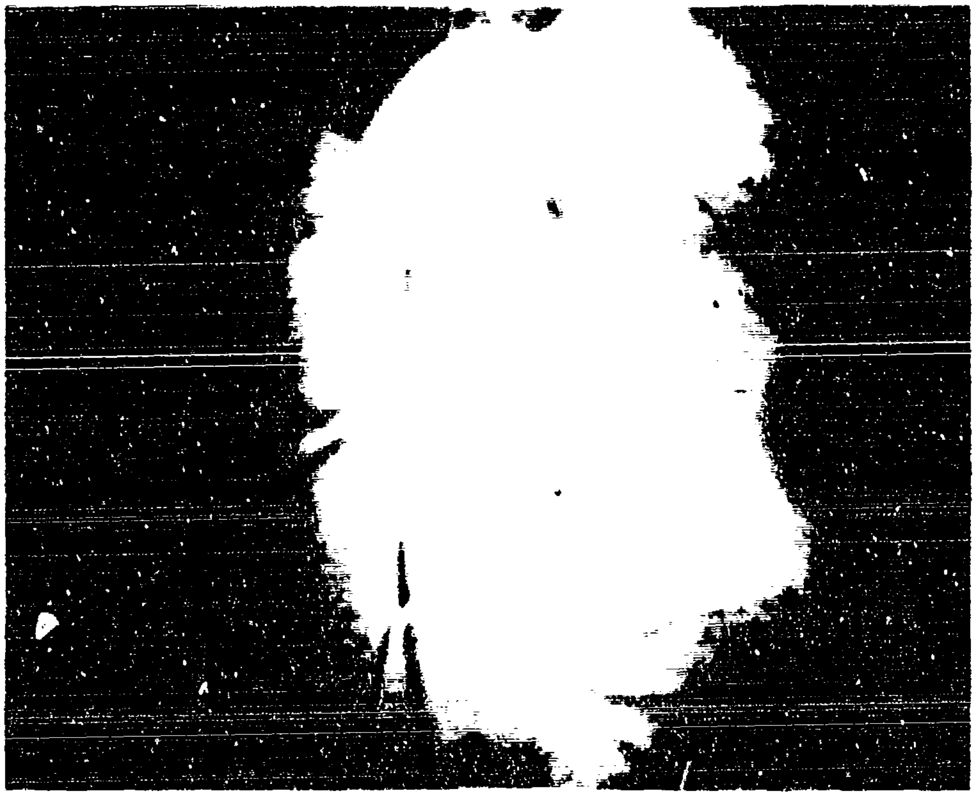

FIGURE 8. A fundus photograph of a rhesus monkey retina exposed to 50% of the energy required to produce a lesion.

FIGURE 9. The restrained rhesus monkey in the audiometric evaluation test situation.

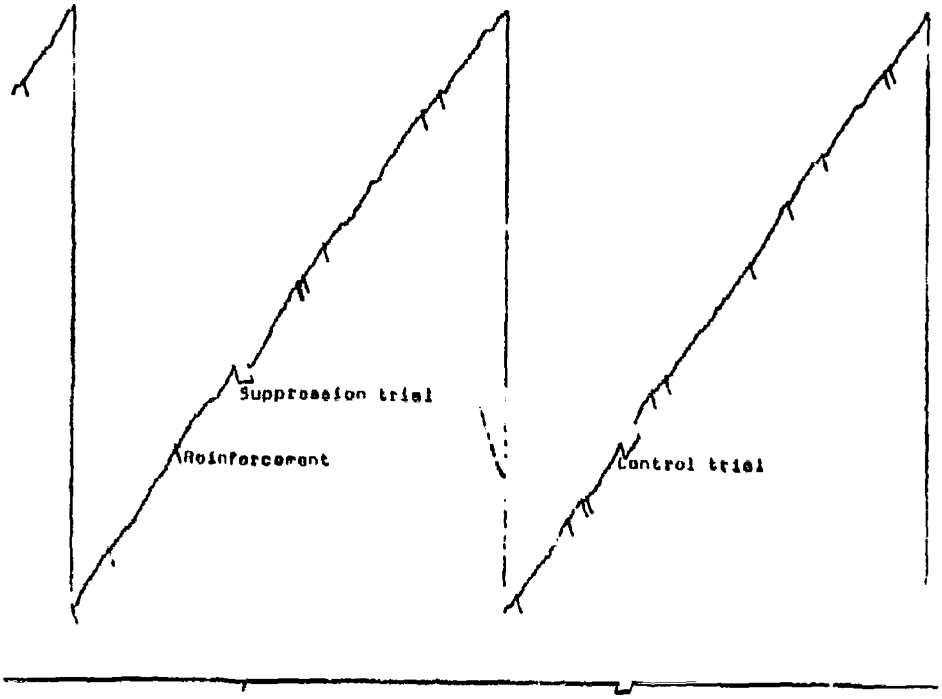

FIGURE 10. Level pressing behavior and tone discrimination record from the audiometric test situation.

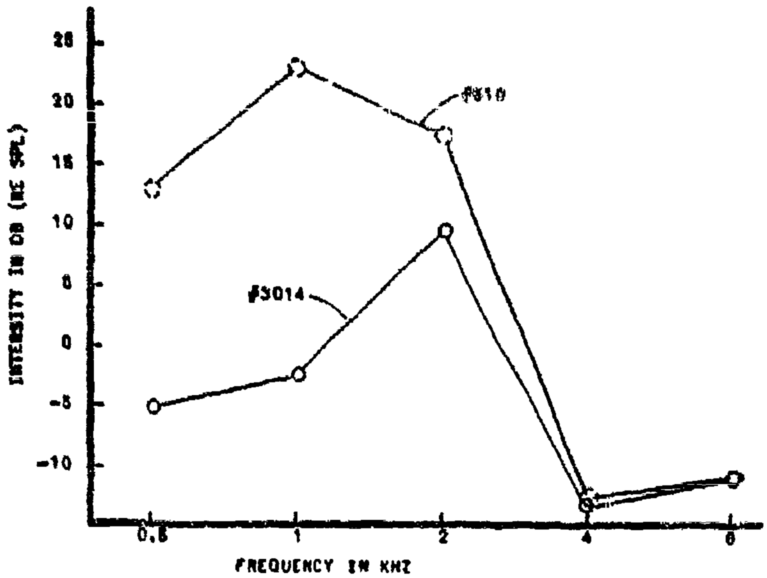

FIGURE 11. Examples of two audiograms.

hazardous environments ~~have been~~ discussed. These methods yield quantifiable data that allow rather accurate determinations of the magnitude of the insult (from lethal to barely detectable), as well as the duration, of the behavioral change.

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